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CARDIOVASCULAR BENEFITS OF GLP-1 RECEPTOR AGONISTS: EVIDENCE FROM CARDIOVASCULAR OUTCOMES TRIALS (CVOTs)

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ABSTRACT

Cardiovascular disease remains the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM). In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as an important therapeutic class capable of providing cardiovascular benefits beyond glycemic control. This review aimed to evaluate the current evidence regarding the cardiovascular effects of GLP-1RAs, with particular emphasis on findings from major cardiovascular outcome trials (CVOTs).

A narrative review of randomized controlled trials, meta-analyses, and contemporary clinical guidelines was conducted. Major CVOTs evaluating lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide, oral semaglutide, and efpeglenatide were analyzed with respect to major adverse cardiovascular events (MACE), cardiovascular mortality, stroke, myocardial infarction, heart failure, and renal outcomes.

The available evidence demonstrates that several GLP-1RAs significantly reduce cardiovascular risk in patients with T2DM. Liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide consistently showed reductions in MACE, while meta-analyses confirmed favorable effects on cardiovascular mortality, all-cause mortality, and stroke. Additional benefits included improved renal outcomes and clinically meaningful weight loss. Recent evidence from the SELECT trial further suggests that cardiovascular protection may extend to individuals with overweight or obesity without diabetes.

In conclusion, GLP-1 receptor agonists have evolved from glucose-lowering agents into therapies with established cardioprotective properties. Their ability to improve cardiovascular outcomes and reduce cardiometabolic risk supports their central role in contemporary diabetes management and cardiovascular prevention strategies.

KEYWORDS

GLP-1 Receptor Agonists; Type 2 Diabetes Mellitus; Cardiovascular Outcomes; Cardiovascular Disease; Obesity; Semaglutide

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Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM), despite substantial advances in glucose-lowering therapies and cardiovascular prevention strategies [3]. Individuals with T2DM exhibit a two- to fourfold increased risk of developing cardiovascular complications compared with the general population, and cardiovascular events account for a significant proportion of premature deaths and healthcare expenditures worldwide [3]. Although intensive glycemic control reduces the risk of microvascular complications, its impact on macrovascular outcomes has historically been modest, emphasizing the need for therapeutic strategies capable of addressing both metabolic abnormalities and cardiovascular risk [1,3].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as one of the most important therapeutic classes in contemporary diabetes management. Initially developed as glucose-lowering agents, GLP-1RAs exert their effects through glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and promotion of satiety, resulting in improved glycemic control and clinically meaningful weight reduction [1,2]. Beyond these metabolic effects, accumulating evidence suggests that GLP-1RAs possess pleiotropic properties that may contribute to cardiovascular protection. Experimental and clinical studies have demonstrated favorable effects on endothelial function, vascular inflammation, oxidative stress, lipid metabolism, blood pressure regulation, and atherosclerotic plaque stability [1,2].

The cardiovascular implications of antidiabetic therapies gained increasing attention following concerns regarding the cardiovascular safety of several glucose-lowering agents. In response, regulatory authorities, including the United States Food and Drug Administration (FDA), mandated dedicated cardiovascular

outcome trials (CVOTs) to evaluate the cardiovascular safety of newly approved antidiabetic medications. These large-scale randomized controlled trials have fundamentally transformed the understanding of diabetes treatment by shifting the focus from glycemic control alone toward comprehensive cardiovascular risk reduction [5].

Since 2015, multiple CVOTs have investigated the cardiovascular effects of various GLP-1 receptor agonists in patients with T2DM and elevated cardiovascular risk. These studies have evaluated agents including lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide, oral semaglutide, and efpeglenatide. Collectively, the findings have demonstrated that several members of the GLP-1RA class not only meet cardiovascular safety requirements but also significantly reduce major adverse cardiovascular events (MACE), cardiovascular mortality, and adverse renal outcomes [5,6].

Meta-analyses integrating data from these trials have provided robust evidence supporting a class-wide cardiovascular benefit of GLP-1 receptor agonists. Pooled analyses have demonstrated significant reductions in MACE, cardiovascular death, all-cause mortality, and stroke, while simultaneously confirming favorable effects on renal outcomes [5,6]. Importantly, the magnitude of cardiovascular protection observed in several studies appears greater than would be expected solely from improvements in glycemic control, suggesting the involvement of additional biological mechanisms [2,5].

Despite the growing body of evidence supporting the cardioprotective effects of GLP-1RAs, important questions remain regarding the relative efficacy of individual agents, the consistency of benefits across different patient populations, and the mechanisms underlying cardiovascular risk reduction. Furthermore, differences in study design, baseline cardiovascular risk, duration of follow-up, and pharmacological characteristics of individual compounds may influence the interpretation of available evidence [1,6].

Therefore, the aim of this review is to critically evaluate the evidence derived from major cardiovascular outcome trials investigating GLP-1 receptor agonists and to assess their impact on cardiovascular risk reduction in patients with type 2 diabetes mellitus. Particular emphasis is placed on the effects of individual agents on major adverse cardiovascular events, cardiovascular mortality, myocardial infarction, stroke, heart failure, and renal outcomes, as well as on the potential mechanisms responsible for the observed cardiovascular benefits.

Methodology

This study was conducted as a narrative literature review aimed at evaluating the cardiovascular benefits of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with type 2 diabetes mellitus (T2DM), with a particular focus on evidence derived from cardiovascular outcome trials (CVOTs). The review sought to synthesize current knowledge regarding the impact of GLP-1RAs on major adverse cardiovascular events (MACE), cardiovascular mortality, myocardial infarction, stroke, heart failure, and renal outcomes, while also exploring the potential mechanisms responsible for the observed cardioprotective effects.

The methodology was based on the principles of evidence-based medicine (EBM), emphasizing the use of high-quality scientific evidence derived from randomized controlled trials, systematic reviews, meta-analyses, and contemporary clinical recommendations. Particular attention was paid to publications that have significantly contributed to the current understanding of the role of GLP-1 receptor agonists in cardiovascular risk reduction and cardiometabolic disease management [1–6].

Data collection involved a comprehensive review of key publications addressing the cardiovascular effects of GLP-1RAs in adult patients with T2DM. The literature included studies investigating the mechanisms of action of GLP-1 receptor agonists, their metabolic and cardiovascular effects, and their clinical application in contemporary diabetes care [1,2]. Additional emphasis was placed on publications evaluating cardiovascular risk among patients with T2DM and on studies assessing the impact of GLP-1RA therapy on cardiovascular outcomes and disease progression [3,4]. Furthermore, evidence from systematic reviews and meta-analyses was incorporated to provide a broader assessment of the consistency and magnitude of cardiovascular benefits observed across multiple clinical trials [5,6].

The review focused on clinically relevant outcomes reported in the available literature, including major adverse cardiovascular events, cardiovascular mortality, all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, and composite renal outcomes. In addition, data concerning body weight reduction, glycemic control, and other cardiometabolic risk factors were considered when relevant to the interpretation of cardiovascular benefits. Information regarding study populations, therapeutic interventions, duration of follow-up, and reported outcomes was analyzed to identify recurring patterns and areas of agreement within the available evidence.

A qualitative synthesis of the collected data was performed. Findings from individual studies were compared with pooled estimates reported in systematic reviews and meta-analyses to evaluate the overall effect of GLP-1RA therapy on cardiovascular and renal outcomes. Particular attention was given to the consistency of results across different GLP-1 receptor agonists and patient populations, as well as to the biological mechanisms proposed to explain cardiovascular risk reduction. The evidence was interpreted within the context of current clinical practice and evolving treatment strategies aimed at reducing cardiovascular morbidity and mortality among patients with T2DM [4–6].

By integrating evidence from mechanistic studies, large clinical trials, and contemporary evidence syntheses, this review provides a comprehensive assessment of the cardiovascular effects of GLP-1 receptor agonists and their emerging role as cardiometabolic therapies with benefits extending beyond glycemic control.

Results

A total of eight major cardiovascular outcome trials (CVOTs) evaluating the cardiovascular safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RAs) were included in this review [7–14]. Together, these randomized controlled trials enrolled more than 60,000 patients with type 2 diabetes mellitus (T2DM), representing one of the largest evidence bases among contemporary glucose-lowering therapies. The populations studied varied substantially with respect to baseline cardiovascular risk, ranging from patients with established atherosclerotic cardiovascular disease (ASCVD) to individuals with multiple cardiovascular risk factors but no prior cardiovascular events. Follow-up periods ranged from 1.3 to 5.4 years, allowing for comprehensive assessment of both short- and long-term cardiovascular outcomes.

The ELIXA trial was the first dedicated CVOT conducted in the GLP-1RA class and enrolled 6,068 patients with T2DM who had recently experienced an acute coronary syndrome [7]. The primary composite endpoint included cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. Lixisenatide demonstrated cardiovascular safety by meeting the predefined non-inferiority criteria; however, no significant reduction in major adverse cardiovascular events (MACE) was observed compared with placebo. Rates of hospitalization for heart failure and other cardiovascular outcomes were similarly unaffected. Although ELIXA did not demonstrate superiority, its findings provided reassurance regarding the cardiovascular safety profile of GLP-1RAs and established the foundation for subsequent outcome trials.

More convincing evidence emerged from the LEADER trial, which evaluated liraglutide in 9,340 patients with T2DM and high cardiovascular risk [8]. Approximately 81% of participants had established cardiovascular disease at baseline. During a median follow-up of 3.8 years, liraglutide significantly reduced the risk of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Importantly, the reduction in MACE was accompanied by a 22% reduction in cardiovascular mortality and a 15% reduction in all-cause mortality. Liraglutide also reduced the incidence of nephropathy-related outcomes, particularly new-onset persistent macroalbuminuria. These findings were among the first to demonstrate that a glucose-lowering agent could provide substantial cardiovascular protection independent of its effects on glycemic control.

The SUSTAIN-6 trial subsequently investigated semaglutide in 3,297 patients with T2DM at high cardiovascular risk [9]. Despite a shorter follow-up period compared with LEADER, semaglutide was associated with a significant reduction in MACE. The cardiovascular benefit was primarily driven by a marked reduction in non-fatal stroke, while favorable trends were observed for myocardial infarction and cardiovascular mortality. Semaglutide also demonstrated significant renal benefits, reducing the incidence of new or worsening nephropathy. Notably, a higher incidence of diabetic retinopathy complications was observed among semaglutide-treated patients, particularly in those experiencing rapid improvements in glycemic control. Nevertheless, the overall benefit-risk profile remained favorable and further strengthened the evidence supporting GLP-1RA-mediated cardiovascular protection.

The EXSCEL trial evaluated once-weekly exenatide in 14,752 patients, representing one of the largest studies conducted within the GLP-1RA class [10]. Approximately 73% of participants had established cardiovascular disease. Exenatide demonstrated cardiovascular safety and showed a trend toward reduction in MACE; however, superiority over placebo was not achieved. Despite the absence of statistically significant reductions in the primary endpoint, all-cause mortality appeared lower in the exenatide group. The neutral findings observed in EXSCEL may be partly explained by relatively high treatment discontinuation rates and lower adherence compared with other CVOTs.

The HARMONY Outcomes trial evaluated albiglutide in 9,463 patients with T2DM and established cardiovascular disease [11]. During a median follow-up of 1.6 years, albiglutide significantly reduced the risk

of MACE compared with placebo. The magnitude of risk reduction was among the largest reported in the GLP-1RA class and was achieved despite relatively modest effects on glycemic control and body weight. These findings provided additional support for the hypothesis that GLP-1RAs exert direct cardiovascular effects beyond glucose lowering alone.

The REWIND trial expanded the evidence base by examining dulaglutide in a broader patient population [12]. Unlike previous CVOTs, only approximately one-third of participants had established cardiovascular disease, while the majority were enrolled based on multiple cardiovascular risk factors. Over a median follow-up of 5.4 years, the longest among GLP-1RA CVOTs, dulaglutide significantly reduced the incidence of MACE. Importantly, the consistency of benefit across subgroups suggested that cardiovascular protection may extend beyond secondary prevention to include patients at elevated cardiovascular risk without prior cardiovascular events. Dulaglutide also demonstrated favorable renal effects, including reduced progression of albuminuria and preservation of kidney function.

The PIONEER 6 trial evaluated the first oral formulation of semaglutide in 3,183 patients with T2DM and high cardiovascular risk [13]. Although the trial was primarily designed to establish cardiovascular safety rather than superiority, oral semaglutide demonstrated a favorable cardiovascular profile. Reductions in cardiovascular death and all-cause mortality were observed, although the study was not sufficiently powered to detect statistically significant differences in the primary endpoint. Nevertheless, the results supported the cardiovascular safety of oral semaglutide and suggested that the benefits observed with injectable formulations may also extend to oral administration.

Further evidence supporting a class effect was provided by the AMPLITUDE-O trial, which evaluated efpeglenatide in 4,076 patients with T2DM and either cardiovascular disease or chronic kidney disease [14]. Efpeglenatide significantly reduced MACE and demonstrated substantial renal benefits. Importantly, cardiovascular protection was observed despite widespread background use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, indicating that GLP-1RAs may provide additive benefits when combined with other cardioprotective therapies.

When the results of all major CVOTs were considered collectively, a consistent pattern of cardiovascular benefit emerged [15,16]. Meta-analyses demonstrated that GLP-1RA therapy reduced the risk of MACE by approximately 12–14%, cardiovascular mortality by 12–13%, and all-cause mortality by approximately 12%. Furthermore, treatment was associated with a significant reduction in the incidence of non-fatal stroke, representing one of the most consistent findings across trials. Although reductions in myocardial infarction were generally less pronounced, the overall effect favored active treatment.

Beyond traditional cardiovascular endpoints, GLP-1RAs demonstrated clinically relevant renal benefits [8,9,12,14–16]. Across studies, treatment reduced the risk of composite renal outcomes, primarily through prevention of macroalbuminuria and slowing progression of diabetic kidney disease. These observations suggest that cardiovascular and renal protection may be mediated through overlapping biological mechanisms, including improvements in endothelial function, reductions in oxidative stress and systemic inflammation, and attenuation of atherosclerotic progression.

The effects of GLP-1RAs on heart failure outcomes were comparatively modest [15,16]. While some individual trials reported reductions in hospitalization for heart failure, pooled analyses generally indicated a neutral or mildly beneficial effect. This contrasts with the more pronounced heart failure benefits observed with SGLT2 inhibitors and suggests that the cardiovascular advantages of GLP-1RAs are primarily driven by anti-atherosclerotic and anti-inflammatory mechanisms rather than direct effects on cardiac hemodynamics.

Overall, the available evidence consistently demonstrates that GLP-1 receptor agonists significantly improve cardiovascular outcomes in patients with T2DM. The strongest evidence supports reductions in MACE, cardiovascular mortality, all-cause mortality, stroke, and adverse renal outcomes. Among individual agents, liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide demonstrated the most robust cardiovascular benefits, whereas lixisenatide and exenatide primarily established cardiovascular safety. Collectively, these findings have transformed the therapeutic role of GLP-1RAs from glucose-lowering agents to key components of contemporary cardiovascular risk reduction strategies.

Discussion

The present review highlights the substantial impact of GLP-1 receptor agonists (GLP-1RAs) on cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM). Over the past decade, the management of T2DM has evolved from a predominantly glucocentric approach toward a broader cardiometabolic strategy focused on reducing cardiovascular morbidity and mortality. This paradigm shift has been largely driven by evidence from cardiovascular outcome trials demonstrating that several GLP-1RAs confer clinically meaningful cardiovascular protection beyond their glucose-lowering effects [17,18].

One of the most important observations arising from the available evidence is the consistency of cardiovascular benefit across multiple GLP-1RA molecules. Although the magnitude of risk reduction varies between individual agents, the overall direction of effect has been remarkably uniform. Significant reductions in major adverse cardiovascular events (MACE) have been reported for liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide, suggesting that cardiovascular protection represents a class effect rather than an isolated property of a single compound [17,18]. These findings have led to the incorporation of GLP-1RAs into international guidelines for cardiovascular risk reduction in patients with T2DM and established atherosclerotic cardiovascular disease.

The mechanisms underlying the cardioprotective effects of GLP-1RAs remain an area of active investigation. While improved glycemic control undoubtedly contributes to reductions in vascular complications, the magnitude of cardiovascular benefit observed in clinical trials appears disproportionate to the relatively modest reductions in glycated hemoglobin levels. This observation suggests that additional biological mechanisms play a significant role in mediating cardiovascular protection. Experimental studies have demonstrated that GLP-1 receptor activation exerts anti-inflammatory, anti-atherogenic, and vasculoprotective effects. Improvements in endothelial function, reductions in oxidative stress, attenuation of vascular inflammation, and stabilization of atherosclerotic plaques have all been proposed as potential mechanisms contributing to reduced cardiovascular risk [17].

Weight loss may represent another key contributor to the cardiovascular benefits of GLP-1RA therapy. Obesity is strongly associated with insulin resistance, hypertension, dyslipidemia, systemic inflammation, and accelerated atherosclerosis. By promoting satiety and reducing caloric intake, GLP-1RAs facilitate clinically meaningful reductions in body weight. Recent studies evaluating higher-dose semaglutide have demonstrated average weight reductions exceeding those historically achieved with pharmacological obesity treatments, highlighting the potent metabolic effects of this therapeutic class [19]. Improvements in body composition and reductions in visceral adiposity may further contribute to cardiovascular risk reduction through favorable effects on metabolic and inflammatory pathways.

An interesting finding emerging from cardiovascular outcome trials is the differential effect of GLP-1RAs on specific cardiovascular endpoints. Meta-analyses have consistently shown a particularly pronounced reduction in stroke risk, whereas the reduction in myocardial infarction tends to be more modest. The reasons for these differences remain incompletely understood but may reflect variations in the pathophysiological mechanisms underlying cerebrovascular and coronary artery disease. Improvements in endothelial function, blood pressure control, and vascular inflammation may exert stronger effects on cerebral circulation than on established coronary atherosclerosis, thereby contributing to the observed differences in clinical outcomes [17,18].

The effect of GLP-1RAs on heart failure outcomes appears less pronounced than their impact on atherosclerotic cardiovascular disease. Unlike sodium-glucose cotransporter-2 (SGLT2) inhibitors, which consistently reduce hospitalization for heart failure, GLP-1RAs have generally demonstrated neutral or only modest benefits in this setting. This distinction suggests that the cardiovascular advantages of GLP-1RAs are primarily mediated through anti-atherosclerotic mechanisms rather than direct effects on cardiac hemodynamics. Consequently, current treatment strategies increasingly emphasize the complementary use of GLP-1RAs and SGLT2 inhibitors in patients at particularly high cardiovascular risk [17,18].

The renal benefits associated with GLP-1RA therapy also deserve consideration. Although the nephroprotective effects of GLP-1RAs are generally less pronounced than those observed with SGLT2 inhibitors, reductions in albuminuria and slower progression of diabetic kidney disease have been consistently reported across multiple clinical trials. Preservation of renal function is clinically important, as chronic kidney disease substantially increases cardiovascular risk and contributes to adverse long-term outcomes in patients with T2DM. The ability of GLP-1RAs to provide simultaneous cardiovascular and renal protection further supports their role as cardiometabolic therapies rather than conventional glucose-lowering agents [17].

Another important aspect concerns the expanding therapeutic applications of incretin-based therapies. Recent investigations have demonstrated that the benefits of GLP-1 receptor activation extend beyond diabetes management. The STEP clinical trial program showed that semaglutide produces substantial and sustained weight loss in individuals with overweight or obesity, establishing a new standard for pharmacological obesity treatment [19]. Furthermore, the development of dual incretin receptor agonists such as tirzepatide has generated considerable interest because of their ability to achieve even greater reductions in body weight and improvements in metabolic parameters [20]. These findings suggest that future cardiovascular prevention strategies may increasingly target obesity as a primary therapeutic objective.

Perhaps the most significant recent development in this field has been the publication of the SELECT trial. Unlike previous CVOTs, which focused primarily on patients with T2DM, SELECT evaluated semaglutide in overweight and obese individuals without diabetes. The trial demonstrated a significant reduction in major cardiovascular events, providing the first direct evidence that GLP-1RA-mediated cardiovascular protection can occur independently of glucose lowering [21]. These findings support the hypothesis that weight reduction, improvements in systemic inflammation, and modulation of cardiovascular risk factors contribute substantially to the observed cardioprotective effects. Moreover, the results of SELECT may redefine the role of GLP-1RAs in cardiovascular medicine and potentially expand their indications beyond traditional diabetes care.

Despite the substantial progress achieved in recent years, several limitations of the available evidence should be acknowledged. Considerable heterogeneity exists among cardiovascular outcome trials with respect to study populations, baseline cardiovascular risk, trial duration, and pharmacological characteristics of individual agents. Differences in molecular structure, receptor affinity, and treatment adherence may influence the magnitude of cardiovascular benefit observed across studies. Additionally, several trials were primarily designed to establish cardiovascular safety rather than superiority, limiting the statistical power available for evaluating individual cardiovascular outcomes.

Future research should focus on clarifying the mechanisms responsible for cardiovascular protection, identifying patient populations most likely to benefit from therapy, and determining the optimal integration of GLP-1RAs with other cardioprotective agents. Further studies evaluating newer incretin-based therapies, including dual and triple receptor agonists, may provide additional insights into the relationship between metabolic control, weight reduction, and cardiovascular risk.

In conclusion, GLP-1 receptor agonists have emerged as one of the most important therapeutic advances in contemporary cardiometabolic medicine. Evidence from randomized controlled trials demonstrates significant reductions in major adverse cardiovascular events, cardiovascular mortality, stroke, and renal complications. The recent expansion of evidence into populations without diabetes further supports the concept that GLP-1RAs should be viewed as cardiometabolic therapies with broad applications in cardiovascular prevention. As the understanding of incretin biology continues to evolve, these agents are likely to play an increasingly prominent role in the prevention and management of cardiovascular disease.

Conclusions

The evidence generated from cardiovascular outcome trials over the past decade has fundamentally transformed the understanding and clinical application of glucagon-like peptide-1 receptor agonists (GLP-1RAs). Initially introduced as glucose-lowering therapies for the management of type 2 diabetes mellitus (T2DM), GLP-1RAs have evolved into a therapeutic class with proven cardiovascular and renal benefits. The results of large-scale randomized controlled trials and subsequent meta-analyses have consistently demonstrated that several GLP-1RAs significantly reduce the incidence of major adverse cardiovascular events (MACE), cardiovascular mortality, and all-cause mortality while simultaneously improving renal outcomes in patients with T2DM [15,16].

A key finding emerging from the available evidence is that the cardiovascular benefits of GLP-1RAs extend beyond improvements in glycemic control alone. While reductions in glycated hemoglobin undoubtedly contribute to improved clinical outcomes, the magnitude of cardiovascular risk reduction observed in cardiovascular outcome trials cannot be fully explained by glucose lowering. Current evidence suggests that multiple mechanisms are involved, including clinically meaningful weight loss, improvements in blood pressure and lipid profiles, attenuation of systemic inflammation, enhancement of endothelial function, and stabilization of atherosclerotic plaques [15–18]. The integration of these effects likely contributes to the substantial reductions in cardiovascular events observed across diverse patient populations.

Another important conclusion arising from this review is the consistency of cardiovascular benefit across several members of the GLP-1RA class. Although differences in efficacy exist among individual agents, the overall body of evidence supports a class-wide cardioprotective effect. Liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide have all demonstrated significant reductions in cardiovascular risk, providing clinicians with multiple evidence-based therapeutic options [15,16]. These findings have led to a major shift in treatment recommendations, with contemporary international guidelines now advocating the use of selected GLP-1RAs not only for glycemic management but also for cardiovascular risk reduction in patients with T2DM and established atherosclerotic cardiovascular disease or elevated cardiovascular risk [17,18].

The expanding role of GLP-1RAs in obesity management further strengthens their importance within modern cardiometabolic medicine. Obesity is increasingly recognized as a chronic disease and a major contributor to cardiovascular morbidity and mortality. Recent clinical trials have demonstrated that semaglutide and newer incretin-based therapies can achieve unprecedented levels of weight reduction, resulting in significant improvements in multiple cardiovascular risk factors [19,20]. These observations highlight the close relationship between obesity, metabolic dysfunction, and cardiovascular disease and suggest that effective weight management may become a central component of future cardiovascular prevention strategies.

A particularly important development has been the demonstration of cardiovascular benefit in individuals without diabetes. The SELECT trial provided the first direct evidence that semaglutide reduces major cardiovascular events in overweight and obese patients without T2DM, thereby expanding the therapeutic potential of GLP-1RAs beyond traditional diabetes care [21]. This landmark finding suggests that the cardiovascular benefits of GLP-1RAs are not solely dependent on improvements in glycemic control but may instead reflect broader effects on cardiometabolic health. As a result, the distinction between antidiabetic therapy and cardiovascular prevention is becoming increasingly blurred, and GLP-1RAs are emerging as therapies with applications across multiple medical specialties.

Despite these advances, several challenges remain. Long-term real-world effectiveness, cost-effectiveness, treatment adherence, and accessibility continue to influence the implementation of GLP-1RA therapy in routine clinical practice. Furthermore, important questions remain regarding the optimal timing of treatment initiation, the comparative efficacy of individual agents, and the identification of patient subgroups most likely to derive the greatest cardiovascular benefit. Additional research is also needed to clarify the mechanisms underlying cardiovascular protection and to determine the potential advantages of newer dual- and triple-incretin receptor agonists currently under investigation [20].

Future studies should focus on expanding the evidence base in populations traditionally underrepresented in cardiovascular outcome trials, including younger individuals, patients with earlier stages of metabolic disease, and those without established cardiovascular disease. Further investigation is also warranted to determine whether the cardiovascular benefits observed with GLP-1RAs can be enhanced through combination therapy with other cardioprotective agents, particularly sodium-glucose cotransporter-2 inhibitors. Such approaches may offer opportunities for more comprehensive management of cardiometabolic risk and further reductions in cardiovascular morbidity and mortality.

In summary, GLP-1 receptor agonists represent one of the most significant therapeutic advances in contemporary cardiovascular and metabolic medicine. Robust evidence from randomized controlled trials, meta-analyses, and recent obesity-focused studies demonstrates that these agents provide substantial benefits extending far beyond glycemic control. By reducing cardiovascular events, improving renal outcomes, promoting sustained weight loss, and potentially preventing cardiovascular disease in high-risk individuals without diabetes, GLP-1RAs have redefined the standards of care for patients with cardiometabolic disease. As ongoing research continues to broaden the understanding of incretin biology and therapeutic applications, GLP-1RAs are likely to assume an even greater role in future strategies aimed at reducing the global burden of cardiovascular disease and improving long-term patient outcomes [15–21].

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